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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,739	12/24/2003	Nabil Hanna	037003-0307368 1997-30-05	9111
909 7590 01/22/2007 PILLSBURY WINTHROP SHAW PITTMAN, LLP P.O. BOX 10500 MCLEAN, VA 22102			EXAMINER DAVIS, MINH TAM B	
			ART UNIT 1642	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/743,739

Applicant(s)

HANNA ET AL.

Examiner

MINH-TAM DAVIS

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**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 08 December 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).


4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: none.  
Claim(s) objected to: none.  
Claim(s) rejected: 47, 51-65 and 68.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.  
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). 12/08/06  
13. ☐ Other: \_\_\_\_\_.

  
SHANON FOLEY  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

Continuation of 5. Applicant's reply has overcome the following rejection(s): 112, second paragraph and 112, first paragraph, written description and scope of enablement.

***DETAILED ACTION***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 48-50, 66-67.

Accordingly, claims 47, 51-65, 68 are being examined.

***Specification***

The amendment of the specification of 12/08/06 is acknowledged and entered.

***Obviousness-type Double Patenting***

Claims 47, 51-65, 68 of the instant application remain non-provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-2, 4-19 of US Application Serial No. 09/853581, now US patent No. 6,998,125, for reasons already of record in paper of 09/08/06.

The response asserts that a terminal disclaimer executed by the undersigned will be considered when allowable claims have been noted.

The rejection remains, for reasons already of record in paper of 09/08/06. The issue of execution of a terminal disclaimer however will be delayed until the time of allowance, if the examined claims were allowable.

***Claim Rejections - 35 USC § 112 First Paragraph, New matter***

Claim 64 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons already of record in paper of 09/08/06.

The response asserts as follows:

The paragraph on page 12 of the application that contains the sentences cited by the examiner goes on to describe that: "It is preferred that such peptides are completely absent from the antigen formulation, despite their apparent stimulation of the humoral compartment of the immune system. That is, although such peptides may enhance the humoral response, they are disadvantageous when a cytotoxic T-lymphocyte response is desired." (See page 12, lines 12-16). The paragraph beginning on line 8 of page 12 thus describes the invention wherein peptides such as MDP are completely absent as a "preferred embodiment," it describes that peptides such as MDP can provide the advantage of enhancing the humoral response, and it expressly describes that more than 20 micrograms of a peptide such as MDP interferes with induction of a CTL response. One of skill in the art would clearly understand that the description on page 12 of the importance that an MDP be "lacking" from the adjuvant formulation of the invention does not simply describe complete absence of MDP from the adjuvant formulation, but also describes the method of the invention in which MDP is present in an amount sufficiently low (i.e., < 20 micrograms per normal human formulation administration) that the MDP does not interfere with induction of a CTL response. One of skill in the art would therefore understand from the description provided by the specification that the disclosed invention includes and can be practiced as a method wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating MDP.

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The response has been considered but is not found to be persuasive for the following reasons:

The specification only teaches not to use the muramyl dipeptide, and its properties, i.e. it will interfere with induction of a CTL response if it provided in an amount greater than about 20 micrograms. There is nothing in the specification to teach or suggest to use an antigen formulation containing no more than 20 micrograms of an immunostimulatory muramyl dipeptide in the claimed method for enhancing an antigen-specific cytotoxic T cell lymphocyte. Although a method wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating MDP can be practiced, such method is not taught or suggested by the specification. The subject matter claimed in claim 46 broadens the scope of the invention as originally disclosed in the specification.

***Claim Rejections - 35 USC § 103***

A. Claims 47, 51-63, 65, 68 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri et al (US 5,695,770, filed on 06/07/1995), in view of Woodworth C D et al, June 1996 (Cell Growth & Differentiation, 7: 811-820), and Segarini et al (WO 94/09815, of record), and as evidenced by Schmolka et al, 1977 (J Am Oil Chem Soc, 54: 110-116, IDS #JJR submitted on 12/12/05), for reasons already of record in paper of 09/08/06.

The response asserts that the claimed invention is surprising and unpredictable.

The response asserts that Raychaudhuri et al (US 5,695,770) do not teach the claimed invention, and that the cited references do not provide suggestion or motivation to modify the method of Raychaudhuri et al with a reasonable expectation of success.

The response asserts that at the time the invention was made, there were conflicting reports on the ability of TGFbeta-1 to inhibit growth of HPV-positive cells. The response asserts that as described by Woodworth et al., at the time the invention was made, TGFbeta was known to inhibit the growth of some HPV-immortalized cell lines, and to induce other HPV-immortalized cell lines to undergo apoptosis (see p. 817, right column). The response recited newly submitted abstracts of the references by Braun et al, Jacobberger et al, Rorke et al, and Ozbun et al asserting that they teach that TGFbeta **inhibits growth or induces apoptosis** in HPV-immortalized cells. The response asserts that Braun et al. (Mol. Carcinog., 1992, 6(2): 100-111, abstract attached) teach that TGFbeta inhibits the growth of HPV-immortalized cells that are resistant to in vitro differentiation signals. The response asserts that Jacobberger et al. (Exp. Cell Res., 1995, 220(2):390-6, abstract attached) similarly teaches that growth of HPV-immortalized cervical cells in vitro is inhibited by TGF[3, and Rorke et al. (Exp. Cell Res., 1995, 216(1):65-2, abstract attached) describes an HPV16-immortalized cervical cell line that induced by TGF[3 to undergo apoptosis. The response asserts that Ozbun et al. (J. Virol., 1996, 70(8):5437-46) states that there are "conflicting reports on the ability of TGF[31 to inhibit the growth of HPV- positive keratinocytes in monolayer cultures,". The response asserts that it describes a tissue culture system "that more accurately mimics the in vivo cellular environment and architecture," and it teaches that TGFbeta-1 promotes the differentiation of HPV-positive keratinocytes in said tissue culture system. The response asserts that in view of such conflicting teaching, one would not have expected the **contrary results** when modifying the method of Raychaudhuri et al, by adding an inhibitor of TGF-beta, i.e. **stimulating growth** of HPV E7 expressing **tumor cells** in treated subject.

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The submission of the abstracts of the references by Braun et al, Jacobberger et al, Rorke et al, and Ozburn et al is acknowledged and entered.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, the claimed invention is not surprising and unpredictable for the following reasons:

Although Woodworth et al teach that TGFbeta was known to inhibit the growth of **some** HPV-immortalized cell lines, and to induce other HPV-immortalized cell lines to undergo apoptosis, Woodworth et al teach that immortalization of keratinocytes with HPV **frequently** results in loss of growth inhibition by TGF-beta (see p. 817, right column, second paragraph). Woodworth et al further teach that under **conditions that induce squamous differentiation**, TGF-beta-1 promotes growth of HPV-immortalized cells (p.817, first column, p.812, second column, and figure 2 on page 813). Woodworth et al teach that differentiation results in decrease in binding of EGF to receptors, and that TGF-beta up-regulates EGF receptor, and thus stimulates proliferation of immortalized cells (p.817, first column). Woodworth et al teach that HPV-immortalized cells exhibit aberrant epithelial differentiation, resembling cervical dysplasia, and thus HPV-immortalized cells are relevant model for malignant transformation (p.812, first column, second and third paragraph).

The submitted abstracts however do not describe the growth conditions in which the HPV-immortalized cells are treated and inhibited by TGF-beta. The submitted abstracts do not provide or support evidence that under **conditions that induce squamous differentiation**, which conditions are more closely related to cervical dysplasia, as taught by Woodworth et al,



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TGF-beta-1 inhibits growth of HPV-immortalized cells. On the contrary, the teaching of Woodworth et al clearly clarifies why conditions that induce squamous differentiation are necessary for the **growth induction** phenomena of TGF-beta-1 in HPV-immortalized cells, by teaching the mechanism by which TGF-beta-1 works, supra.

One would have a reasonable expectation of success when combine HPV 16 E7 antigen taught by Raychaudhuri et al with an inhibitor of TGF-beta taught by WO 94/09815, for use in the method of enhancing CTL response in cancer cells, such as cervical cancer, taught by Raychaudhuri et al, because TGF-beta enhances growth of HPV-immortalized cells under conditions that induce squamous differentiation, which conditions resemble cervical dysplasia, and providing a relevant to model for malignant transformation, as taught by Woodworth et al, and because an inhibitor of TGF-beta is expected to suppress in the activity of TGF-beta, including the activity of enhancing growth of HPV-immortalized cells. One would have motivated to do so, because a combination of an inhibitor of TGF-beta and a vaccine increase the immune response of the vaccine, as taught by WO 94/09815.

**B.** The amended claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri et al (US 5,695,770, filed on 06/07/1995), in view of Woodworth C D et al, June 1996 (Cell Growth & Differentiation, 7: 811-820), and Segarini et al (WO 94/09815, of record), and as evidenced by Schmolka et al, 1977 (J Am Oil Chem Soc, 54: 110-116, IDS #JJR submitted on 12/12/05), and further in view of Schultz-Cherry et al, 1995 (JBC, 270 (13): 7304-7310) or Capon DJ et al (WO 91/08298).

It is noted that claim 49 is cancelled, and the embodiment of claim 49 is now incorporated into the amended claim 47.

The response asserts that the added references do not alleviate the deficiency of the combined teaching of Raychaudhuri et al (US 5,695,770), Woodworth et al, WO 94/09815, and Schmolka et al, i.e. no motivation or suggestion to modify the method of Raychaudhuri et al with a reasonable expectation of success.

The response has been considered but is not found to be persuasive for the following reasons:

The claimed invention is clearly obvious over the teaching of Raychaudhuri et al (US 5,695,770), Woodworth et al, WO 94/09815, and Schmolka et al, supra.

Further, it would have been obvious to replace the anti-TGF-beta antibodies in the method taught by Raychaudhuri et al (US 5,695,770), Woodworth et al, Capon et al, WO 94/09815, and Schmolka with another TGF-beta antagonist, such as the thrombospondin peptide GGWSHW taught by Schultz-Cherry et al or a TGF-beta receptor linked to a constant region of an immunoglobulin, taught by WO 91/08298, because using the thrombospondin peptide GGWSHW or the TGF-beta receptor linked to a constant region of an immunoglobulin provides alternative treatment methods, and thus increasing the versatility of the treatment methods.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS

January 17, 2007

  
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